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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,709	05/05/2006	Felicia Grases Freixedas	OFICINA-256657	5118

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EXAMINER	
CHANNAVAJJALA, LAKSHMI SARADA	
ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
12/20/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/595,709	GRASES FREIXEDAS, FELICIA	
	Examiner	Art Unit	
	Lakshmi S. Channavajjala	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *8-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of RCE dated 1-20-10 and amendment dated 10-19-09 is acknowledged.

Claims 8-19 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1-20-10 has been entered.

In response to the amendment, the previous rejection of record has been withdrawn and the following new rejection has been applied:

Claim Rejections - 35 USC § 103

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 8-19 are rejected under 103(a) as being unpatentable over Grases et al (Effect of crystallization inhibitors on vascular calcifications induced by vitamin D: A Pilot study in Sprague-Dawley rats. Cir. J. 2007; 71:1152-1156; submitted on PTO-1449 dated 5-8-06), as evidenced by Horrobin et al. (Us patent 5,516,801) and further in view of Bissett et al. (US Patent 5,821,237) and Kamiya et al. (US Patent Application Pub. No. 2003/0119910).

Grases et al. teach that pathological calcification in soft tissues (i.e.ectopic clacification) can have severe consequences when it occurs in vital organs such as the vascular or renal systems (see especially page 1152, col. 1, first para.). Grases et al. teach that in general, the development of tissue clacification requires a preexisting injury as an inducer (heterogenous nucleant), whereas further progression requires the presence of other promoter factors (such as hypercalcemia and/or hyperphosphatemia) and/or a deficiency in calcification repressors factors (crystallization inhibitors and cellular defense mechanisms); see page 1152, col. 1, second para.). Grases et al. teach that pyrophosphate, biphosphonates and phytate (myo-inositol hexakisphosphate) have been shown to inhibit crystallization in the form of vascular calcification (page 1152, col. 2, last para.). Grases et al. also teach that based on the fact that phytate was found to act as vascular calcification inhibitor, the action of polyphosphates could be important in protecting against vascular calcification (page 155, last para.). Grases teaches oral route of administering phytate and not the claimed topical route; and further employs 1% phytate.

While instant claims require topical administration of phytate, the claims do not recite the actual amount of phytate and further only states “pathological calcification treating effective amounts” of phytate. The examples in the instant specification recite 2.9%; 0.7% and 2.5% (pages 7-9) for topical application.

Horrobin et al. is added as an evidentiary reference to show that ectopic calcifications involve various soft tissues, including blood vessels, kidney, skin, and brain (col. 2, lines 14-32).

Grases does not teach topical application of phytic acid as required by the instant claims.

Bissett et al. teach methods of treatment for improving the visual appearance of skin comprising administering topical compositions comprising myoinositol compounds, wherein said topical compositions are in the forms such as lotions, creams and ointments (abstract, and col. 6, line 35 to col. 8, line 52; col. 13, lines 29-59). Bissett et al. teach that methods comprising **topically applying to the skin an effective amount of the compositions in a subject so as to deposit an effective amount of the primary actives (e.g. myoinositol compound such as myo-inositol hexakisphate dodecasodium salt and phytic acid) on the skin**, wherein the primary actives are left in contact with the skin for a period of at least several hours e.g. about 4 to about 12 hours); the compositions may be applied from about three times a day to about once every other day (col. 23, line 66 to col. 24, line 38; see also col. 4, line 43 to col. 8, line 51). In particular, Bissett et al. exemplify compositions comprising phytic acid in a **concentration range of 1 to 5 %** (cols. 25, line 40 to col. 27, line 49). Also, Bissett et al. disclose a regimen for applying said compositions to the skin one time per week at a level of 5 mg/cm2 over a three-year period to regulate skin wrinkles.

Bissett fails to teach phytic acid for treating calcification in soft tissues. However, Kamiya et al. teach methods of treating or preventing aging-associated diseases caused by a decrease in the expression of Klotho protein in animals or humans, including aging, ectopic calcification, skin involution, arteriosclerosis, hyperlipidemia, hypertension, cerebral apoplexy, diabetes, senile dementia of Alzheimer type (para

0022-0023). In particular, Kamiya et al. teach compositions comprising phosphorus containing compounds, such as phytic acid, for treating said diseases in animals or humans (abstract; para. 0081). Also, Kamiya et al. disclose that it is desirable to administer said compositions by any desirable route that is most effective for the treatment, including non-oral routes (para. 0044). Kamiya teaches an amount of 0.5% to 5% or more per unit dry weight of food or feed drink.

Although Kamiya et al. teach methods of treating aging associated diseases (e.g. **ectopic calcification**) in an animal or human comprising administering a composition containing phytic acid by non-oral routes, this reference does not specifically teach the instantly claimed method step of topically applying the myo-inositol hexaphosphate (= phytic acid) composition to treat/prevent pathological calcifications.

It would have been obvious to a person of skill in the art at the time the invention was made to not only administer phytic acid of Grases by oral route but further modify the route of administration of the composition Grases by applying said composition topically to skin as taught by Bissett et al., with an expectation to treat or prevent a pathological calcification in a soft tissue (e.g. ectopic calcification) as taught by Kamiya et al. One would have been motivated to do so because Kamiya et al. suggest that compositions comprising phytic acid can be administered by any desirable route, including non-oral routes such as subcutaneous methods, Grases teaches 1% phytic acid in oral route is effective in reducing the calcium and phosphorus deposits in kidneys; and further the method of topically applying phytic acid compositions to the skin as taught by Bissett et al. is also a non-oral route. Further, one would reasonably

expect that the topical administration/application to the skin of a composition comprising the instantly claimed myo-inositol hexaphosphate (phytic acid) as taught by the Kamiya et al. and Bissett et al. would be absorbed by the skin and then travel via the bloodstream to the target site where the calcification is generated, including the subepithelial tissue, renal tissue, pulmonary tissue, cerebral tissue, and the wall of a blood vessel because both Kamiya et al. and Bissett et al. teach therapeutically effective compositions and it is well known that drugs that are applied to the skin do get absorbed by the skin and then get distributed throughout the body via the bloodstream. Besides, both Kamiya et al. and Bissett et al. teach compositions for treating aging-associated conditions (e.g. skin wrinkles), which overlaps with the instant claimed population (i.e. ectopic calcification) as evidenced by the teaching of Kamiya et al. and Horrobin et al. and also Grases such that one would expect that administration of the same drug (phytic acid) as taught by the prior art to the same instantly claimed population (ectopic calcification) would also have the same therapeutic effects absence evidence to the contrary.

With respect to the new limitation “therapeutic” method, it is the position of the examiner that it is implicit that the topical application of phytic acid in the teachings of Kamiya (per the suggestion of Bissett) would implicitly result in a therapeutic treatment.

It is noted that the instant application discloses that ectopic calcifications are common alterations associated with soft tissues, mainly skin, kidney, tendons, and cardiovascular tissues (page 1, lines 16-18).

It is also noted that applicant exemplifies compositions comprising sodium phytate 2.9% (2% phytate), sodium phytate 0.7% (0.5% phytate), sodium phytate 2.5% (1.7% phytate), which overlap with the above referenced teaching of Bissett et al. of concentrations of phytic acid in the range of from 1-5% of phytic acid (see specification, pages 7-9).

With respect to the preamble of claim 14, it is noted that Kamiya et al. teach methods for preventing aging-associated diseases, including ectopic calcification, comprising administering compositions comprising phytic acid (para. 0081).

With respect to the limitations recited in dependent claims 9-13 and 15-19, it is noted that Kamiya et al. teach aging-associated diseases including ectopic calcification, which overlaps with the instant claimed population (pathological calcification in a soft tissue). Since ectopic calcification involves soft tissues, including skin, brain, kidney, and blood vessels, one would reasonably expect that the method of treatment comprising topically administering the same instantly claimed compound as taught by the prior art would also be effective in treating/ preventing pathological calcification involving subepithelial tissue, renal tissue, pulmonary tissue, cerebral tissue, and the wall of a blood vessel as evidenced by the teaching of Horrobin et al. (col. 2, lines 14-32).

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to Arguments

3. Applicant's arguments filed 10-19-09 have been fully considered but they are not persuasive.

Applicants argue that according to Kamiya et al., one skilled in the art would infer that ornithine or a salt thereof is the active ingredient used for treating or preventing a disease caused by a decrease in the expression level of Klotho protein and that the remaining components are pharmaceutically acceptable carriers or additional active ingredients for another therapeutic purpose (see para. 40). Therefore, it cannot be stated that phytic acid is an active ingredient used for treating or preventing a disease caused by a decrease in the expression level of Klotho protein (e.g. ectopic calcification) since the active ingredient for treating such calcification is ornithine or a salt thereof. It is argued that in order to clearly distinguish the present invention from Kamiya's disclosure, the term "as an active ingredient" has been added to claims 8 and 14 showing that the present compositions use myo-inositol hexaphosphate as an active ingredient for the claimed purpose.

Applicants' argument is not persuasive because the rejection is not made over the teachings over Kamiya et al. alone and even if Kamiya fails to teach phytic acid as an active ingredient, Grases teaches phytic acid as an effective agent for reducing calcifications. Instant rejection now employs the teachings of Grases et al, which teaches phytic acid for the same treatment, except in a different route of administration. Therefore, a skilled artisan does not need to modify the teaching of Kamiya to arrive at the instant claims and instead the rejection proposes modification of the teachings of

Grases based on the teachings of Bissett, Kamiya and also as evidenced by Horrobin. Therefore, the argument that one would not reasonably expect to select ectopic calcification from the laundry list of possible diseases prevented or treated under the heading "disease caused by a decrease in the expression of Klotho protein as taught by Kamiya et al. for treatment with compositions comprising a phosphorous containing compound (e.g. phytic acid) is not persuasive. Further, it is noted that Kamiya et al. provides a general teaching of diseases associated with a decrease in the expression of Klotho protein in animals or humans (e.g. aging, ectopic calcification, skin involution, osteoporosis, alopecia; paras. 0022-0026) such that one would reasonably expect that the genus of diseases associated with a decrease in the expression of Klotho protein in animals or humans would be representative of the various species encompassed by said genus since each disease/condition species of the genus is associated with a decreased level Klotho protein.

Applicants state that topical administration is not obvious at all because the references show the difficulty for drugs to be delivered transdermally, according to the abstract of Kannikkannan et al (exhibit A- pages 593, 594 and table 1) and further highlight the remarks of Tanner and Marks on page 250 that a great majority of xenobiotics penetrate extremely slowly certianly insufficiently to be useful from a therapeutic stand point. It is argued that the molecular size, polarity of drug and other physicochemical properties of the permeant dictate the permeation of the drug. It is argued that in light of the evidence form the articles of Kannikkannan et al, Mark & Tanner, Prausnitz et al and Brown, one skilled in the art would not have found that

topical administration would be preferable and certainly not obvious in light of the teachings of Kamiya et al. alone or in combination with Bissett et al. In addition, applicant maintains that Bissett only discusses the cosmetic use of a composition comprising myoinositol compounds. There is no reference in the whole disclosure about a "disease" or "disorder" and the wording "cosmetically acceptable derivatives thereof" is widely used through the text (see, for example, col. 2, lines 26 and 48; col. 3, lines 11, 29 and 40; col. 9, lines 5, 6, 17, 27 and 55; .col. 10, lines 29, 37, 41, 47 and 48 and also the section where the term "cosmetically acceptable carrier" is explained). Applicant argue that the definition of "cosmetic" includes articles intended to be rubbed, poured, sprinkled and sprayed and that Bissett only teaches cosmetic use that is for visual appearance and superficial effect whereas a drug for provides systemic effect. It is argued cosmetic effect is local and not systemic.

Applicants arguments are not persuasive because the cited prior art teaches the same “effective amounts” of phytic acid for topical application in Bissett. Instant claims also require topical application and the claims and Bissett's teaching are not different in terms of the very application of the composition to the skin, which per applicants' own admission and also the instant disclosure includes gels, lotions, creams etc. Thus, applicants have not shown how the same active agent of the prior art, when applied in the same method such as that disclosed and claimed in the instant, does not result in the argued systemic absorption. It should be noted that Bissett teaches phytic acid application to the skin topically for cosmetic effect. The mere fact that the prior art does not describe another advantage (that is inherent to the prior art composition) does not

negate the property i.e., ability of the compound to be absorbed systemically. Therefore, even though Bissett and Kamiya et al fail to teach that phytic acid is absorbed to reach systemic circulation, the effect would have been expected by a skilled artisan because Kamiya suggests that phytic acid can be administered topically for therapeutic (even if it is suggested as an additional component) effect and not cosmetic effect. Kamiya et al. teach methods of treating diseases/conditions associated with Klotho protein, wherein said conditions/diseases may be preferably prevented/treated with compositions comprising ornithine and at least one compound selected from the group consisting of compounds containing a divalent cationic metal and compounds containing phosphorus (e.g. phytic acid = phosphorus containing compound; para. 0078-0081) and Bissett et al. teach methods of treating skin wrinkles (= condition associated with aging skin; col. 1, lines 17-67) comprising topical depositing (= applying) on the skin of a subject a composition comprising a skin repair active agent (e.g. phytic acid = phosphorus containing compound; col. 3, line 2 to col. 8, line 51; and cols. 25-26, Examples 2-7). Applicants have not shown that phytic acid of Bissett or Kamiya et al does not enter systemic circulation. Further, applicant has not provided any objective evidence to show that the method of treatment encompassed by the prior art does not work for treating ectopic calcifications or skin aging conditions.

Finally, in the response dated 2-5-08, page 6, applicants admit that phytate administered topically is effective for decreasing mineral deposits in hearts and arteries. References which do not qualify as prior art because they postdate the claimed invention may be relied upon to show the level of ordinary skill in the art at or around the

time the invention was made. Ex parte Erlich, 22 USPQ 1463 (Bd. Pat. App. & Inter. 1992). Further, in certain circumstances, references cited to show a universal fact need not be available as prior art before applicant's filing date. In re Wilson, 311 F.2d 266, 135 USPQ 442 (CCPA 1962). Such facts include the characteristics and properties of a material or a scientific truism. Some specific examples in which later publications showing factual evidence can be cited include situations where the facts shown in the reference are evidence "that, as of an application's filing date, undue experimentation would have been required. In re Corneil, 347 F.2d 563, 568, 145 USPQ 702, 705 (CCPA 1965). Thus, by applicants' own admission topical application of phytic acid (Kamiya or Bissett) is effectively absorbed in to systemic circulation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakshmi S. Channavajjala whose telephone number is 571-272-0591. The examiner can normally be reached on 9.00 AM -5.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611